Glucose and insulin responses to dietary chromium supplements: a meta-analysis[1–3]

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ABSTRACT

Background: Several authors, mostly on the basis of nonrandomized studies, have suggested dietary trivalent chromium supplementation as an attractive option for the management of type 2 diabetes and for glycemic control in persons at high risk of type 2 diabetes.

Objective: The study aimed to determine the effect of chromium on glucose and insulin responses in healthy subjects and in individuals with glucose intolerance or type 2 diabetes.

Design: The study design was a systematic review and meta-analysis of randomized clinical trials (RCTs).

Results: The authors identified 20 reports of RCTs assessing the effect of chromium on glucose, insulin, or glycated hemoglobin (Hb A_{1c}). This review summarizes data on 618 participants from the 15 trials that reported adequate data: 193 participants had type 2 diabetes and 425 were in good health or had impaired glucose tolerance. The meta-analysis showed no association between chromium and glucose or insulin concentrations among nondiabetic subjects. A study of 155 diabetic subjects in China showed that chromium reduced glucose and insulin concentrations; the combined data from the 38 diabetic subjects in the other studies did not. Three trials reported data on Hb A_{1c}: one study each of persons with type 2 diabetes, persons with impaired glucose tolerance, and healthy subjects. The study of diabetic subjects in China was the only one to report that chromium significantly reduced Hb A_{1c}.

Conclusions: Data from RCTs show no effect of chromium on glucose or insulin concentrations in nondiabetic subjects. The data for persons with diabetes are inconclusive. RCTs in well-characterized, at-risk populations are necessary to determine the effects of chromium on glucose, insulin, and Hb A_{1c}. *Am J Clin Nutr* 2002;76:148–55.

KEY WORDS Chromium, dietary supplements, diabetes, insulin, glucose, hemoglobin, meta-analysis

INTRODUCTION

Both genetic and dietary factors influence the manifestation of type 2 diabetes. Randomized clinical trials show conflicting evidence as to the effect of chromium deficiency on the emergence of type 2 diabetes (1–25 and H Lukaski, unpublished observations, 2000). Nonetheless, second to calcium, chromium is the largest-selling mineral supplement in the United States: ≈10 million Americans take chromium supplements, sometimes for the prevention or treatment of diabetes (26).

Although early case series reported that chromium alleviates severe symptoms of diabetes (27–32), whether randomized placebo-controlled clinical trials have adequately confirmed the findings from uncontrolled studies (33–37) remains controversial. Four recent literature reviews summarized evidence supporting chromium as a nutraceutical that controls glucose and insulin concentrations (9, 12, 15, 16) but provided no quantitative overview. In addition, these reviews did not separate the discussion of randomized controlled trials from the discussion of uncontrolled or observational studies, rendering interpretation of the true effect of chromium supplementation difficult to assess. Although Hellerstein (10) critically reviewed randomized clinical trials of chromium supplementation and diabetes, he presented only a qualitative description of the findings. To help elucidate the effect of dietary chromium, we performed a systematic review of the literature and a meta-analysis of randomized clinical trials assessing the effect of dietary chromium supplements on measures of glycemic control in healthy subjects and in individuals with glucose intolerance or type 2 diabetes.

METHODS

Eligibility criteria

Trials were eligible for inclusion if the participants (healthy adults or those with glucose intolerance or type 2 diabetes) were randomly assigned to dietary chromium supplementation or a control, either placebo or active (such as picolinate or yeast). For crossover designs, the analysis included data only from the first period to allow incorporation of the data into the meta-analysis.

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Received February 2, 2001.

Accepted for publication July 3, 2001.

Identification of trials

We performed a computerized bibliographic search of the Cochrane Controlled Trials Register (April 2000; Cochrane Collaboration, Oxford, United Kingdom) and MEDLINE (1966 to May week 3, 2000; National Library of Medicine, Bethesda, MD) in all languages. For both databases, we applied the optimal MEDLINE search strategy for identifying controlled clinical trials (38) along with the following specific search terms: *chromium, diabetes, glucose, insulin,* and *hemoglobin* A_{1c}. We then inspected the bibliographies of the collected articles to identify additional relevant reports. Two persons (NEJ and MDA) independently read the title, abstract, and descriptors of each article to identify potentially relevant trials for full review, and copies of these articles were obtained.

Data collection and statistical analysis

We considered trials to be randomized only if the text stated explicitly that the intervention was allocated randomly. Two of the authors (NEJ and MDA) reviewed and abstracted all potentially relevant articles independently and resolved disagreement by consensus or by third party adjudication (JTW). If necessary, we contacted the investigator for further information on methodology or data. Reviewers were not blinded to author. All contacted investigators were asked whether they had or knew of additional data relevant for this review.

Using a specially designed form, the reviewers abstracted data on study design, methodologic quality (39), and glucose, insulin, and glycated hemoglobin (Hb A_{1c}) concentrations after the intervention. The data were then entered into a FILEMAKER PRO (version 4.0; Claris Corporation, Santa Clara, CA) database and exported to SAS (version 6.12; SAS Institute Inc, Cary, NC) for data analysis and to S-PLUS 2000 (Math Soft, Inc, Seattle) for graphics.

The difference between means (and the 95% CIs of the difference) of glucose, insulin, and Hb A_{1c} concentrations was calculated for each trial. For studies with more than one chromium arm or more than one placebo arm, we calculated a weighted average of response rates if the groups were similar by assigning each arm a weight proportional to its sample size. We considered dissimilar groups to be separate treatments. Pooled mean differences and 95% CIs for studies of diabetic and nondiabetic subjects were calculated by using 2 different fixed-effects models: weighted mean differences and standardized mean differences. We planned to report only the results from the weighted mean difference model unless the models yielded dissimilar results. A chi-square test was used to assess heterogeneity among trials. If the P value was <0.05, which indicated heterogeneity among studies, and if only 1 or 2 studies explained the heterogeneity, we removed those studies from the analysis. Otherwise, in the face of evidence of heterogeneity, we planned to use a random-effects model to combine the data.

Formulation, dose, and level of exercise may affect the relation between dietary chromium and glycemic control. For each of these variables, we used a linear regression model to assess whether the relation between dietary chromium and glycemic control differed among levels of the variable.

RESULTS

We identified 41 potentially relevant reports of randomized clinical trials of dietary chromium supplements: 27 from the 2 electronic databases, 13 from reference sections of published articles, and 1 as yet unpublished paper through contact with an investigator. Of the 41 studies, 21 reported data on glucose, insulin, or Hb A_{1c}. We subsequently found one study to be ineligible because the blood collected for glucose-related endpoints was only voluntary (40). The reports of 5 studies had insufficient data for abstraction (20–24). Because updated data from these trials were not available from the principal investigators, we omitted the trials from the analysis. Two independent reviewers (NEJ and EAL) abstracted data from figures in 2 of the included papers (1, 4). Thus, our analysis includes data from 15 trials (1–8, 11, 13, 14, 18, 19, 25, and H Lukaski, unpublished observations, 2000) with a total of 618 participants, 193 with type 2 diabetes and 425 in good health or with impaired glucose tolerance. In our analyses, we report data from trials that used placebo or other agents as a control. Restricting the analyses only to those studies that used a placebo yielded essentially the same results as those we report in this paper.

The main design features of the 15 randomized clinical trials of dietary chromium supplementation and glucose-related factors are summarized in **Table 1**. Eleven of the 15 trials (73%) used data from ≥90% of the subjects randomly assigned in the outcome analysis (3–5, 7, 11, 13, 14, 17–19, 25). Overall, 15% of the randomly assigned patients were lost to follow-up or were excluded from the analyses.

As seen in **Table 2**, the mean concentration of glucose for nondiabetic subjects was ≈5 mmol/L. Only 4 studies reported chromium concentrations at baseline.

Health status at baseline, chromium formulation, and dose defined important subgroups. Four of the 15 randomized clinical trials summarized in Table 1 included diabetic subjects, for a total of 193 diabetic subjects with analyzable data (1, 3, 6, 25); one study included 155 of these subjects (6). Two studies analyzed subjects who were glucose intolerant at baseline; one study enrolled only intolerant subjects ($n = 24$; 4) and the other enrolled 5 glucose-intolerant and 27 healthy subjects (14). For this review, we combined the data from the healthy subjects and from those with glucose intolerance and refer to these subjects as *nondiabetic subjects*. Chromium chloride and chromium picolinate were the most frequently used formulations before and after 1990, respectively.

Anderson et al (6) reported data on 155 diabetic subjects in China, who were randomly assigned to 3 groups: one-third each to 200 μg chromium picolinate, 1000 μg chromium picolinate, and placebo. We excluded this study from the formal meta-analysis for 2 reasons. First, as the only study conducted in a non-Western country, it may represent the effect of supplementation in a chromium-deficient population. Second, including it in the meta-analysis led to P values for heterogeneity below or very close to 0.05. Therefore, the meta-analysis included only 38 diabetic subjects.

Efficacy of dietary chromium supplementation for reducing glucose concentrations

Fasting glucose

All 14 trials reported data on fasting glucose concentrations ($n = 38$ diabetic and 425 nondiabetic subjects; **Table 3**). Combining all 14 trials showed a pooled mean difference in fasting glucose concentrations of 0.027 mmol/L (95% CI: −0.09, 0.15 mmol/L) with no evidence of heterogeneity ($P = 0.97$) (**Figure 1**). Similarly, dietary chromium supplementation was not associated with

TABLE 1
Design features of randomized clinical trials of dietary chromium supplementation and glucose-related factors[1]

First author and reference	Year	Analyzed: randomly assigned	Study population	Country	Chromium dose (formulation)	Control group or groups	Maximum follow-up	Estimated person-years of follow-up	Age range	Blinding
		n (%)			*μg*			*y*	*y*	
Trials with sufficient data										
Offenbacher (1)	1980	24:36 (67)	ND, D	US	10.8 (Brewer's yeast)	Torula yeast	8 wk	3.7	63–93	Single
Offenbacher (17)	1985	23:23 (100)	ND	US	200 ($CrCl_3$)	Brewer's yeast, placebo	10 wk	2.9	63–86	Not clear
Urberg (18)	1987	16:16 (100)	ND	US	200 ($CrCl_3$), 200 ($CrCl_3$+nic)	Nicotinate	28 d	1.3	≥65	Not specified
Abraham (3)	1992	76:76 (100)	ND, D	Israel	250 ($CrCl_3$)	Placebo	6 mo	38.0	42–83	Not specified
Uusitupa (4)	1992	24:26 (92)	I	Finland	160 ("Cr rich" yeast)	Placebo	6 mo	12.0	65–74	Double
Lefavi (5)	1993	34:34 (100)	ND[2]	US	200, 800 (Cr-nic)	Placebo	8 wk	5.2	18–28	Double
Thomas (25)	1996	19:19 (100)	ND, D	US	200 (Cr-nic)	Placebo	8 wk, period 1	2.9	36–60	Double
Anderson (6)	1997	155:180 (86)	D	China	200, 1000 (Cr-pic)	Placebo	4 mo	51.7	35–65	Double
Grant (7)	1997	32:32 (100)	ND[2]	US	400 (Cr-nic), 400 (Cr-pic)	Placebo	9 wk	7.4	18–35	Double
Pasman (8)	1997	33:49 (67)	ND	Nether-lands	200 (Cr-pic)	No supp, CHO	16 mo	44.0	Not specified	Double[3]
Walker (11)	1998	18:20 (90)	ND[2]	US	200 (Cr-pic)	No supp, placebo	14 wk	4.8	18–23	Double[3]
Cefalu (19)	1999	29:29 (100)	ND	US	1000 (Cr-pic)	Placebo	8 mo	19.3	30–74	Double
Crawford (13)	1999	18:20 (90)	ND[2]	US	600 (Cr-niacin)	Placebo	2 mo, period 1	3.0	Not specified	Double
Joseph (14)	1999	32:35 (91)	ND, I[2]	US	1000 (Cr-pic)	Placebo	12 wk	7.4	54–71	Double
Lukaski (unpublished)	2000	85:130 (65)	ND	US	200 (Cr-pic)	Picolinate, placebo	14 wk	17.3	19–51	Double
Trials with insufficient data										
Anderson (20)	1983	76:78 (97)	ND	US	200 ($CrCl_3$)	Placebo	3 mo, period 1	19.0	21–69	Double
Martinez (21)	1985	85:96 (89)	ND, D, I	Canada	200 ($CrCl_3$)	Placebo	10 wk	16.3	58–92	Double
Anderson (22)	1987	8:8 (100)	ND	US	200 ($CrCl_3$)	Placebo	12 wk, period 1	1.8	33–69	Double
Lee (23)	1994	28:30 (93)	D	US	200 (Cr-pic)	Placebo	2 mo, period 1	4.7	32–65	Double
Wilson (24)	1995	26:Not clear	ND	US	220 (Cr-nic)	Placebo	90 d	6.4	Not specified	Double

[1] CHO, carbohydrate supplementation; Cr-nic, chromium nicotinate; Cr-pic, chromium picolinate; D, diabetic; I, impaired glucose tolerance; ND, neither diabetic nor impaired glucose tolerance; No supp, no supplementation.
[2] Exercise intervention.
[3] The no supplementation control group was not blinded.

glucose concentrations among nondiabetic subjects (pooled mean difference: 0.028 mmol/L; 95% CI: −0.086, 0.14 mmol/L).

Four studies of diabetic subjects reported information on fasting glucose concentrations (1, 3, 6, 25). The 1980 study by Offenbacher and Pi-Sunyer (1) and the study conducted by Thomas and Gropper (25), which included data on only 8 and 5 subjects, respectively, showed nonsignificant decreases in fasting glucose concentrations with chromium supplementation (**Table 4**). Abraham et al (3) reported a nonsignificant increase in fasting glucose concentrations (mean difference: 1.17 mmol/L; 95% CI: −1.04, 3.38 mmol/L). Anderson et al (6), who used 2 doses of chromium supplementation, showed a significant decrease in fasting glucose in the group receiving 1000 μg Cr compared with placebo (mean difference: −1.70 mmol/L; 95% CI: −2.41, −0.99 mmol/L) but not in the group receiving 200 μg Cr (mean difference: −0.10 mmol/L; 95% CI: −0.93, 0.73 mmol/L). The small sample size of the studies by Offenbacher and Pi-Sunyer, Thomas and Gropper, and Abraham et al and the noncomparability of the population used for the study by Anderson et al led to inconclusive results concerning the effect of chromium supplementation on fasting glucose concentrations among diabetic subjects.

Glucose at 120 min

Five of the 14 trials reported data on glucose concentrations 120 min after an oral-glucose-tolerance test (n = 8 diabetic and 133 nondiabetic subjects; 1, 4, 7, 14, 19). The overall pooled mean difference was 0.26 mmol/L (95% CI: −0.24, 0.76 mmol/L; test of heterogeneity, P = 0.98). Similarly, dietary chromium supplementation was not associated with 120-min glucose

TABLE 2
Baseline fasting glucose and chromium concentrations[1]

First author and reference	Glucose	Chromium
	mmol/L	
Diabetic		
Offenbacher (1)		
Treatment	5.83 ± 1.67	—
Control	5.27 ± 1.11	—
Abraham (3)		
Treatment[2]	9.71 ± 1.98	3.06 ± 1.37 nmol/L
Control	9.77 ± 2.36	2.29 ± 0.66 nmol/L
Thomas (25)		
Treatment	11.04 ± 5.40	—
Control	12.98 ± 7.69	—
Anderson (6)		
Low dose	10.20 ± 2.18	—
High dose	9.80 ± 2.16	—
Control	9.80 ± 2.12	—
Nondiabetic		
Offenbacher (1)		
Treatment	5.22 ± 0.31	—
Control	4.61 ± 0.47	—
Offenbacher (17)		
Treatment[3]	5.22 ± 0.67	5.39 ± 2.69 nmol/L
Control	5.33 ± 0.54	5.28 ± 1.73 nmol/L
Urberg (18)		
Treatment	5.32 ± 0.53	—
Control	5.24 ± 0.72	—
Abraham (3)		
Treatment[2]	5.77 ± 0.62	2.50 ± 0.99 nmol/L
Control	6.11 ± 0.69	2.88 ± 1.86 nmol/L
Uusitupa (4)		
Treatment[4]	5.30 ± 0.36	0.13 ± 0.11 μg
Control	4.90 ± 0.66	0.13 ± 0.07 μg
Lefavi (5)		
Treatment	5.56 ± 0.47	—
Control	5.61 ± 0.67	—
Thomas (25)		
Treatment	5.70 ± 0.44	—
Control	5.50 ± 0.33	—
Grant (7)		
Treatment	5.09 ± 0.68	—
Control	4.90 ± 0.51	—
Pasman (8)		
Treatment	5.10 ± 0.50	—
Control	5.30 ± 0.50	—
Walker (11)		
Treatment	5.62 ± 1.07	—
Control	4.92 ± 0.73	—
Crawford (13)		
Treatment	5.66 ± 1.33	—
Control	5.11 ± 0.81	—
Joseph (14)		
Treatment	5.73 ± 0.43	—
Control	5.45 ± 0.47	—
Lukaski (unpublished)		
Treatment[2]	4.71 ± 0.49	3.31 ± 0.94 nmol/L
Control	4.66 ± 0.46	2.80 ± 0.80 nmol/L

[1] $\bar{x}$ ± SD.
[2] Mean serum concentrations.
[3] Mean fasting plasma concentrations.
[4] Twenty-four–hour urinary excretion.

among nondiabetic subjects (pooled mean difference: 0.042 mmol/L; 95% CI: −0.43, 0.52 mmol/L).

Two studies reported the relation between chromium and 120-min glucose among diabetic subjects (1, 6). Anderson et al (6) reported a statistically significant reduction in 120-min glucose in the high-dose group compared with the placebo group, but no significant association in the low-dose group. Offenbacher and Pi-Sunyer (1) reported no significant relation between chromium and 120-min glucose (Table 4).

Efficacy of dietary chromium supplementation for lowering insulin concentrations

Fasting insulin

Ten of the 14 trials presented data on fasting insulin concentrations (n = 8 diabetic and 326 nondiabetic subjects; 1, 4, 5, 7, 8, 11, 14, 17, 19, and H Lukaski, unpublished observations, 2000; Table 3). The overall pooled mean difference was 0.28 pmol/L (95% CI: −7.0, 7.5 pmol/L; test of heterogeneity, P = 0.097; **Figure 2**). Dietary chromium supplementation was not associated with insulin concentrations among nondiabetic subjects (pooled mean difference: 0.25 pmol/L; 95% CI: −6.98, 7.48 pmol/L).

Only 2 studies reported the relation between chromium supplementation and fasting insulin in diabetic subjects (1, 6). Offenbacher and Pi-Sunyer (1), in their 8-person subgroup, reported a nonsignificant decrease in fasting insulin concentrations, with a wide CI (mean difference: −71 pmol/L; 95% CI: −267, 124 pmol/L). Anderson et al (6), on the other hand, reported a significant reduction in fasting insulin for both treatment groups compared with placebo, with a mean difference of −23 pmol/L in both groups and identical CIs (95% CI: −30.1, −15.9 pmol/L).

Insulin at 120 min

Five of the 14 trials reported data on insulin concentrations 120 min after an oral-glucose-tolerance test (n = 8 diabetic and 133 nondiabetic subjects; 1, 4, 7, 14, 19). The overall pooled mean difference was 11.1 pmol/L (95% CI: −69.0, 91.2 pmol/L; test of heterogeneity, P = 0.15). Dietary chromium supplementation was not associated with an increase in 120-min insulin among nondiabetic subjects (pooled mean difference: 5.5 pmol/L; 95% CI: −74.0, 85.1 pmol/L).

Only Anderson et al (6) and Offenbacher and Pi-Sunyer (1) reported results for 120-min insulin in diabetic subjects. Offenbacher and Pi-Sunyer (1) showed a nonstatistically significant increase in 120-min insulin concentrations after chromium supplementation, with a wide CI (mean difference: 144 pmol/L; 95% CI: −453, 740 pmol/L). Anderson et al (6) showed identical mean reductions in insulin concentrations for both dose groups compared with placebo, with a mean difference of −63 pmol/L (95% CI for 1000 μg: −79.6, −46.4 pmol/L; 95% CI for 200 μg: −78.3, −47.7 pmol/L). More studies of the effect of chromium supplementation in diabetic populations are needed to clarify these relations.

Efficacy of dietary chromium supplementation for lowering Hb A_{1c}

Three very different trials presented data on Hb A_{1c} concentrations: one study each of 33 healthy subjects (7), 24 persons with glucose intolerance (4), and 155 diabetic subjects (6). The study of healthy subjects reported no association between chromium and Hb A_{1c} concentrations (7). Chromium was associated with a slight, nonstatistically significant reduction in Hb A_{1c} concentrations in the study of glucose-intolerant subjects (mean difference: −0.30%; 95% CI: −0.85%, 0.25%) (4). Anderson et al (6) reported a dose-response relation between dietary chromium supplementation and reduction in Hb A_{1c} concentrations among diabetic subjects (mean

TABLE 3
Postintervention fasting glucose and insulin concentrations in randomized clinical trials[1]

First author and reference	Fasting glucose			Fasting insulin		
	Treatment	Control	Treatment difference	Treatment	Control	Treatment difference
		mmol/L			*pmol/L*	
Offenbacher (1)	5.00 ± 0.58 [12][2]	5.11 ± 0.58 [12]	−0.11 (−0.57, 0.35)[3]	72 ± 124	165 ± 124	−93 (−193, 6)
Offenbacher (17)	5.55 ± 0.89 [8]	5.25 ± 0.47 [15]	0.30 (−0.36, 0.96)	158 ± 115	119 ± 73	39 (−49, 126)
Urberg (18)	5.23 ± 0.68 [10]	5.18 ± 0.65 [5]	0.049 (−0.66, 0.75)	—	—	—
Abraham (3)	7.45 ± 1.96 [40]	7.09 ± 1.30 [36]	0.35 (−0.39, 1.09)	—	—	—
Uusitupa (4)	5.00 ± 0.36 [13]	4.80 ± 0.66 [11]	0.20 (−0.24, 0.64)	136 ± 52	151 ± 48	−14 (−54, 25)
Lefavi (5)	5.11 ± 0.92 [23]	5.22 ± 0.56 [11]	−0.11 (−0.61, 0.39)	76 ± 39	64 ± 20	12 (−8, 32)
Thomas (25)	7.02 ± 2.40 [10]	7.61 ± 3.92 [9]	−0.59 (−3.55, 2.37)	—	—	—
Grant (7)	5.07 ± 0.50 [22]	5.18 ± 0.73 [10]	−0.12 (−0.61, 0.38)	101 ± 41	103 ± 39	−2 (−32, 27)
Pasman (8)	4.70 ± 0.40 [13]	4.70 ± 0.40 [20]	0.00 (−0.28, 0.28)	67 ± 14	74 ± 25	−6 (−20, 7)
Walker (11)	4.92 ± 0.78 [6]	4.96 ± 0.61 [12]	−0.033 (−0.74, 0.68)	101 ± 46	48 ± 12	53 (16, 90)
Cefalu (19)	5.00 ± 1.46 [15]	5.23 ± 1.60 [14]	−0.23 (−1.35, 0.88)	141 ± 183	135 ± 97	6 (−99, 112)
Crawford (13)	4.77 ± 0.77 [8]	5.05 ± 1.07 [10]	−0.28 (−1.13, 0.57)	—	—	—
Joseph (14)	6.01 ± 0.60 [17]	5.78 ± 0.47 [15]	0.23 (−0.14, 0.60)	77 ± 34	82 ± 42	−5 (−32, 22)
Lukaski (unpublished)	4.60 ± 0.47 [26]	4.61 ± 0.46 [59]	−0.006 (−0.22, 0.21)	50 ± 28	50 ± 23	−1 (−13, 11)

[1] Studies are ordered chronologically. Dashes indicate that data were not available. *n* Values are the same for fasting glucose and insulin analyses.
[2] $\bar{x}$ ± SD; *n* in brackets.
[3] $\bar{x}$ (95% CI).

difference for 1000 μg: −1.90%, 95% CI: −2.34%, −1.46%; mean difference for 200 μg: −1.00%, 95% CI: −1.55%, −0.45%).

Analysis of confounders

Chromium supplementation was not associated with fasting insulin or fasting glucose within strata of formulation, dose, or exercise levels.

Safety

None of the 15 trials reported any adverse events associated with dietary chromium supplementation.

DISCUSSION

Encouraging findings in animal and observational studies (15, 41–43) have led many investigators to hypothesize that dietary chromium supplementation may help to control type 2 diabetes or glucose and insulin responses in persons at high risk of diabetes (9, 10, 12, 15, 16). The data from this systematic review show no evidence of a relation between chromium supplementation and concentrations of glucose or insulin in nondiabetic subjects (pooled mean difference for glucose: 0.028 mmol/L; 95% CI: −0.086, 0.14 mmol/L; pooled mean difference for insulin: 0.25 mmol/L; 95% CI: −6.98, 7.48 mmol/L). The individual trials of nondiabetic subjects yielded no association regardless of formulation or dose. Of the studies excluded from this review, only 1 reported an association with better glycemic control (22), whereas 1 excluded randomized clinical trial reported no effect on insulin concentrations (21) and 3 reported no effect on glucose concentrations for all subjects randomly assigned (20, 23, 24). The lack of significant findings among healthy subjects may, in part, be explained by a floor effect; we would expect that glucose and insulin concentrations in healthy subjects could be lowered at most by a small amount.

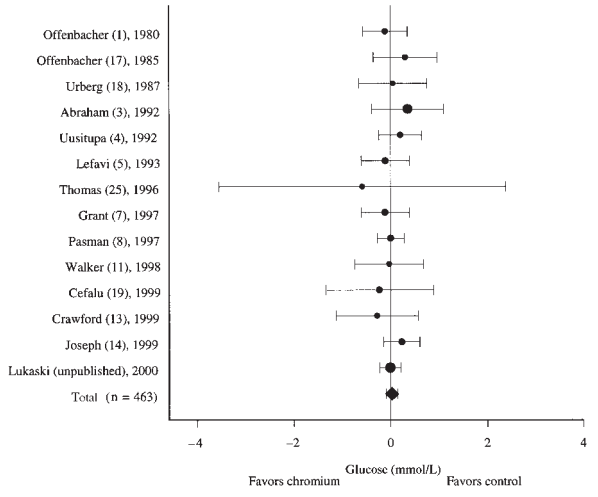

FIGURE 1. Differences in mean fasting glucose concentrations between chromium-treated and control subjects in randomized clinical trials. ●, study-specific mean difference (size of circle corresponds to sample size); ◆, pooled mean difference. Error bars indicate 95% CIs.

The studies included too few patients to make conclusions about the effect of chromium in those with glucose intolerance. Uusitupa et al (4), the only investigators to report findings solely on subjects with impaired glucose tolerance, found no association between dietary chromium supplementation and glucose or insulin concentrations in a study of 24 subjects.

Too few trials in diabetic subjects have been conducted to allow conclusive findings for subjects with type 2 diabetes (1, 3, 6). Anderson et al (6) were the only investigators to report a dose-response relation between chromium and glucose and insulin concentrations in diabetic subjects. Because this study was conducted in China, however, the applicability of the results to the Western hemisphere is uncertain; subjects enrolled had low body mass indexes of 22–23, which may indicate poor nutritional status of the population at baseline. In addition to the study by Anderson et al, only one small randomized controlled trial of chromium supplementation of women with gestational diabetes (n = 20), not included in this review, reported significant reductions in glucose and insulin concentrations in the chromium-supplemented group (44). Three small randomized clinical trials of persons with type 2

TABLE 4
Means, sample sizes, and 95% CIs for studies of diabetic subjects at the maximum follow-up time[1]

First author and reference	Fasting glucose	Glucose at 120 min	Fasting insulin	Insulin at 120 min
	mmol/L	*mmol/L*	*pmol/L*	*pmol/L*
Offenbacher (1)				
Control (n = 4)	5.6	8.7	179	682
Treatment (n = 4)	5.2	11.3	108	825
Treatment − control	−0.4 (−1.2, 0.4)	2.6 (1.2, 4.1)	−71 (−267, 124)	144 (−453, 740)
Abraham (3)				
Control (n = 12)	9.82	—	—	—
Treatment (n = 13)	10.99	—	—	—
Treatment − control	1.17 (−1.04, 3.38)	—	—	—
Thomas (25)				
Control (n = 2)	14.85	—	—	—
Treatment (n = 3)	9.89	—	—	—
Treatment − control	−4.96 (−19.66, 9.73)	—	—	—
Anderson (6)				
Control (n = 50)	8.8	12.3	118	602
Low dose (n = 53)	8.7	12.6	95	539
High dose (n = 52)	7.1	10.5	95	539
Low dose − control	−0.1 (−0.93, 0.73)	0.3 (−0.68, 1.28)	−23 (−30.1, −15.9)	−63 (−78.3, −47.7)
High dose − control	−1.7 (−2.41, −0.99)	−1.8 (−2.68, −0.92)	−23 (−30.1, −15.9)	−63 (−79.6, −46.4)

[1] 95% CI in parentheses. Studies are ordered chronologically. Dashes indicate that data were not available.

diabetes (which included a total of 38 subjects), with data on insulin available for only 8, found no association between chromium supplementation and glycemic control. Two studies not included in the meta-analysis because of insufficient data also reported no association (21, 23).

Glucose and insulin concentrations fluctuate with changes in diet, exercise, and use of some medications. Therefore, measurement of glycated proteins, such as Hb A_{1c}, is a more reliable method of assessing long-term glycemic control (45). Only 3 studies assessed the relation between dietary chromium supplementation and reductions in Hb A_{1c}, one each of healthy subjects (7), subjects with glucose intolerance (4), and diabetic subjects (6). The reduction in Hb A_{1c} concentrations was larger for randomized clinical trials of subjects with more severe disease. Specifically, among diabetic subjects, Anderson et al (6) reported a dose-response relation between dietary chromium supplementation and a decrease in Hb A_{1c} concentrations in the control group compared with the treatment groups (200 and 1000 μg chromium picolinate/d). Reductions in Hb A_{1c} concentrations were evident after 2 mo of chromium supplementation, with more marked reductions after 4 mo. Similarly, Uusitupa et al (4) reported an association of chromium with a reduction in Hb A_{1c} concentrations (0.3%) in subjects with insulin intolerance, but the reduction, which was not statistically significant, was smaller than that reported by Anderson et al among diabetic subjects; however, this association may be attributable to differential weight loss in the treatment groups. In a study not included in this analysis, Jovanovic et al (44) reported that chromium reduced Hb A_{1c} concentrations by 0.4% in women with gestational diabetes receiving 4 μg chromium picolinate/kg body wt for 8 wk compared with a control group (44). The randomized clinical trial of healthy subjects included in this review (7) showed no association of chromium and Hb A_{1c}. These studies assessed the magnitude of change in Hb A_{1c} concentrations. Future studies should also report the number of subjects who shift from abnormal to within-normal ranges for all endpoints.

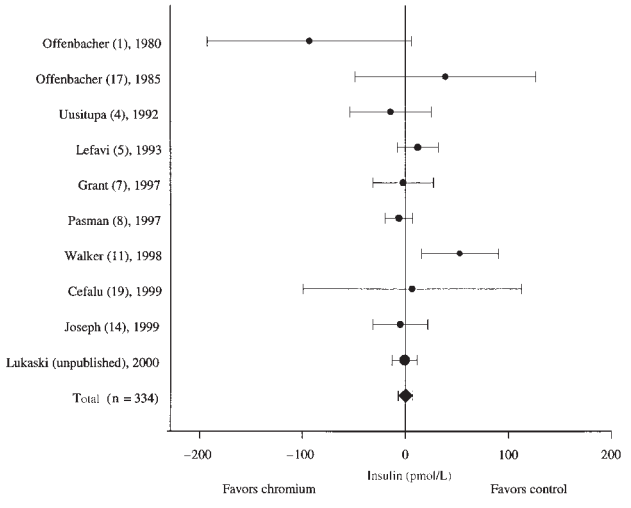

FIGURE 2. Differences in mean fasting insulin concentrations between chromium-treated and control subjects in randomized clinical trials. ●, study-specific mean difference (size of circle corresponds to sample size); ◆, pooled mean difference. Error bars indicate 95% CIs.

The 21 randomized clinical trials either summarized in this review or assessed in this meta-analysis, in which both healthy subjects and persons with type 2 diabetes received between 10.8 and 1000 μg Cr/d for 28 d to 16 mo, reported no evidence of any toxic effect. However, the studies included in this review contribute only an estimated 220 person-years of data (both treated and control groups) and <35 person-years in subjects who received high doses of chromium (≥800 μg). Several case series in the literature have reported chromium toxicity (15). Thus, future studies of chromium supplementation should establish the long-term safety of chromium therapy, particularly at high doses.

This review summarized primarily small, underpowered randomized controlled trials of diverse populations. We reviewed or analytically combined studies of subjects of different nationalities (6, 23), one of which was non-Western (6). Some subjects

were elderly (1, 4, 17, 18, 21), were overweight (7, 8, 14, 19), were athletes (5, 11), were participating in exercise (5, 7, 11, 13, 14) or dietary interventions (13 and H Lukaski, unpublished observations, 2000), had mild forms of diabetes (1), or had atherosclerotic disease (3). Only one of the studies of nondiabetic subjects (13) and no trial of diabetic subjects focused on a large subgroup of older African American women, a segment of the population with a high prevalence of diabetes (46).

It is difficult to recommend whether to launch a large randomized clinical trial in the face of so many unanswered questions. Who is likely to benefit? Currently no biomarker of chromium status exists. What is an efficacious but safe dose? Very few person-years of data are available. Which formulation is best? No single trial has addressed this question. If chromium were a new drug on the pathway to Food and Drug Administration approval, we would recommend a phase II clinical trial, that is, a smaller study with more than one dose or formulation arm. Because the study by Anderson et al (6) has been interpreted as showing some efficacy in diabetic subjects, manufacturers are extensively advertising the benefits of chromium and the general public uses chromium widely. Thus, it is important to either confirm or refute these findings soon with a well-designed study conducted in North America.

Dietary chromium supplements are inexpensive (26), and the limited safety data suggest that chromium is safe even at high doses (6). Thus, if dietary chromium supplementation is efficacious, it would be an attractive option for management of diabetes and for control of insulin and glucose concentrations of persons at high risk of type 2 diabetes. To date, data from randomized clinical trials are sparse and inconclusive. Placebo-controlled randomized clinical trials in well-characterized, at-risk populations are necessary to determine the effects of chromium on concentrations of glucose, insulin, and Hb A_{1c}.

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